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The use of a portable breath analysis device in monitoring type 1 diabetes patients in a hypoglycaemic clamp: Validation with SIFT-MS data

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Dedication:

This article is dedicated to Professor David Smith, a dear friend and teacher of one of the authors (Claire Turner, CT). CT has known David for 13 years and throughout that time he encouraged, helped and supported CT in developing her interest and breath analysis and VOC analysis. David's attention to detail and uncompromising research ethic has enabled the development of SIFT-MS and without his leadership, the area of VOC and breath analysis would be much diminished.

Abstract

Monitoring blood glucose concentrations is a necessary but tedious task for people suffering from diabetes. It has been noted that breath in people suffering with diabetes has a different odour and thus it may be possible to use breath analysis to monitor blood glucose concentration. Here, we evaluate the analysis of breath using a portable device containing a single mixed metal oxide sensor during hypoglycaemic glucose clamps and compare that with the use of SIFT-MS described in previously published work on the same set of patients. Outputs from both devices have been correlated with the concentration of blood glucose in 8 volunteers suffering from type 1 diabetes mellitus. The results demonstrate that acetone as measured by SIFT-MS, and the sensor output from the breath sensing device both correlate linearly with blood glucose, however the sensor response and acetone concentrations differ greatly

between patients with the same blood glucose. It is therefore unlikely that breath analysis can entirely replace blood glucose testing.

Introduction:

Diabetes mellitus is a complex disorder of metabolism which results in prolonged hyperglycaemia unless treated. Treatment involves maintaining blood glucose concentrations within a tight range to maintain health using medication and diet, depending upon the type of diabetes (Kalapos, 2003). However, in order to do this, blood glucose levels must be monitored frequently throughout each day (Evans et al., 1999). This requires taking a small blood sample for analysis using a portable glucose biosensor. However, this deters many diabetes sufferers from monitoring their blood glucose, resulting in poor glycaemic control and the potential for serious complications.

For this reason, there have been many efforts to develop easy, non-invasive, portable and unobtrusive methods of monitoring blood glucose, and many of these methods involve trying to find marker volatile organic compounds which may be present either in breath or from skin which are correlated with blood glucose (Turner, 2011, Wang and Wang, 2013). An obvious candidate is acetone, which is abundant in breath, known to be elevated in diabetes and for which there are numerous analytical techniques.

Another potential volatile biomarker is methyl nitrate (Novak et al., 2007), however, it is present at very low concentrations, which makes it unsuitable as a blood glucose surrogate due to the difficulties in producing a selective, specific and sensitive, portable, low cost and non-invasive monitoring device. So for this reason, monitoring breath acetone is an ideal biomarker if indeed it does show a correlation with blood glucose (Turner, 2011, Wang and Wang, 2013). There have been a number of recent studies to develop sensors for monitoring acetone in breath for this reason (Saraoğlu et al, 2013; Righettoni et al., 2013; Worrall et al., 2013, Deng et al., 2013).

Techniques used for analysing volatile organic compounds (VOCs) in breath or from skin fall into two classes: developmental or research techniques, where the emphasis is on biomarker detection and quantification, and point of care monitoring devices. In the first category falls mass spectrometric techniques, such as selective ion flow tube mass spectrometry (SIFT-MS) (Smith and Spangel, 2011) or PTR-MS (Beauchamp et

al., 2013), GC-MS (Grabowska-Polanowska, 2013) and other similar devices (Amann and Smith, 2013). The second category must be made portable, inexpensive yet sufficiently selective for the VOC(s) of interest. This generally includes devices which make use of gas sensors, including metal oxide sensors (Bârsan et al, 2003; Righettoni et al, 2010), conducting polymer sensors (Yu et al., 2005; Do et al, 2013), FET and MOSFET sensors and optical sensors (Ermanok et al., 2013) and other types. (Zhang et al, 2000; Guo et al., 2010; Saraoglu et al., 2010). Also possible is the development of specific optical sensors, and this technology is rapidly being developed to produce more sensitive and selective sensors for uses such as this with potentially much reduced response times (Wang et al, 2013). When gas sensors are used, they are often assembled into an array in which each sensor responds to different VOCs to a greater or lesser extent, building up a pattern rather than an individual signal for each sample. Such devices are often known as electronic noses (Gardiner and Bartlett, 1994). These devices require some complex algorithms to process data from multiple sensors and carry out pattern recognition to compare to training data sets. In many cases, this is necessary but where a single analyte (e.g. acetone) is involved, this device is overly-complex .

Here, we discuss the use of both a single metal oxide sensor breath analysis device and its comparison with acetone data obtained from SIFT-MS in the analysis of breath. The study was conducted on a number of patients with type 1 diabetes mellitus and blood and breath samples were taken at different blood glucose concentrations in a hypoglycaemic glucose clamp study. Analysis of acetone using SIFT-MS during this study has previously been reported (Turner et al., 2009). This enables the signal from a single sensor to be both assessed against identification and quantification of some of the volatile compounds present as well as against conventionally taken samples for determination of blood glucose. The single sensor greatly simplifies analysis, with no need for complex algorithms to carry out pattern recognition or perform multivariate statistics.

The single metal oxide sensor gas analyser, SMOS-GA, is referred to in this manuscript as “The Breathotron”.

Materials and Methods

The breath analysis device, the Breathotron

The Breathotron is a mains-powered, field-portable instrument housed in a briefcase-sized enclosure (Figure 1). The sensing element is a low cost, single mixed metal oxide semiconductor (MMOS), using a proprietary formulation of chromium-titanium oxide as its responsive element (CAP25, City Technology Ltd, Portsmouth, UK). MMOS as a class are relatively unaffected by the water content of the sample compared with conducting polymer sensors for example, an important consideration in breath analysis (Bârsan et al, 2003).

MMOS, in common with some other classes of gas sensor, have been reported to exhibit significant drift and poor reproducibility (Gardiner and Bartlett, 1994). In addition, they have a long response and recovery time compared to the duration of the human breath. A MMOS exposed to an atmosphere containing VOCs may take several minutes to reach full scale response, and a similar time to recover. The main consequence for the Breathotron design is that no attempt is made to use the full scale response; the sensor is exposed to the breath for a time much shorter than that required to attain full scale response by passing a known volume across it at a carefully controlled flow rate.

The Breathotron was designed to allow samples to be taken from spontaneously breathing subjects, without the need for any particular manoeuvres to be learned and this was achieved by adapting an industrial filter mask (3M 7000S series, 3M United Kingdom plc, Bracknell, UK). The silicone face seal minimises the probability of allergic reaction, covers the nose and mouth and is worn with a full head harness, allowing it to be adjusted to form a seal against the skin of the subject. It incorporates non-return valves at the inlet and outlet and is controlled by a mass flow sensor (AWM720P, Honeywell International Inc., Morristown, NJ, USA) which measures exhaled breath flow rate. This is used to control the sampling sequence of the instrument. The device is operated via software on a Personal Digital Assistant (PDA) which connects to the Breathotron over a serial (RS-232) data link.

Figure 2 shows the general layout of the pneumatic system and summarises the operation of the device. In summary, the MMOS is continually flushed by purified air while not sampling breath. While breath is sampled, the flow in the sampling arm is increased to typically 200 ml min^{-1} , causing exhaled breath to be drawn into the sample loop. If the MMOS is not to be exposed to this breath, the flow in the

sampling arm is reduced to zero at the end of the breath and the instrument returns to standby mode.

If the MMOS is to be exposed to this sample, the sample arm flow is switched off at the end of the breath and the crossover valves simultaneously switch. This causes the sample to be flushed out of the sample loop towards the MMOS by the incoming clean air stream. As the contents of the sample loop pass over the MMOS, the sample loop becomes filled with clean air from the flushing inlet. When this process is complete (typically 5-10s) the crossover valves switch back, returning the instrument to Standby. Using this arrangement the rates of filling and flushing the sample loop can differ while maintaining a constant flow rate across the MMOS at all times.

The gas sensor is housed in a specially machined two-piece aluminium block consisting of a hollow sensor chamber with inlet and outlet sample ports and a flat closing plate with a nitrile gasket to provide a gas-tight seal. The sensor block is heated to prevent breath condensate from collecting inside the sensor chamber using a 20 Watt Peltier thermoelectric heat pump fitted to the block's flat closing plate. A controller circuit maintains block temperature at a nominal 40°C, although this can be set under software control if required. The top also carries a nitrile gasket and is sealed by a printed circuit board carrying the MMOS and preamplifier circuit.

The preamplifier circuit allows the voltage and current in the MMOS to be determined, which are subsequently converted to sensor resistance in software. This signal is then normalised by subtracting the baseline resistance and presented as change in sensor resistance (ΔR) over time (Figure 3). Sensor response data are expressed as maximum excursion of ΔR (ΔR_{max}) following exposure of the MMOS to the sample. Sensor operating temperature was optimised for acetone using 10ppm acetone in synthetic air (SIP Analytical Ltd, Sandwich, Kent, UK). A series of exposures was carried out at temperatures ranging from 360°C to 440°C and the maximum sensor response was observed at 420°C.

Studies were carried out to assess the relationship between sensor response and the vapour phase concentration of a number of different compounds to assess linear range. Acetone, ammonia and propanol were investigated using a concentration range of 0-10ppm (0.1, 0.5, 1, 2, 5 and 10 ppm). Gases were supplied as above in cylinders of certified concentration and diluted as necessary using synthetic air (BOC, Guilford, Surrey) delivered by a gas mixer. This was constructed in-house using two mass flow

controllers (Microflo, Pneuculus Technologies LLC, NH, USA). Flow rates of calibration gas (10 ppm acetone in air as above) and zero grade air were set manually with the aid of a flowmeter (CSI 6000, Cambridge Scientific Instruments, Cambridge, UK) to give the required concentrations. Test samples were produced in Nalophan® gas sampling bags and allowed to equilibrate at laboratory temperature (20 - 22°C) for a minimum of five minutes prior to sampling with the Breathotron.

Insulin clamp details; glucose and insulin infusion.

Full details of the recruitment of patients and the hypoglycaemic clamp study are given in Turner et al. (2009). Briefly, 8 individuals with type 1 diabetes were recruited. Each had a relatively long duration of diabetes (mean 28 ± 3 years) and, on average sub-optimal glycaemic control. Volunteers were admitted to hospital overnight and an insulin clamp technique was used to control plasma glucose values throughout the course of the clamp study. Blood glucose levels were controlled at the appropriate concentration through a primed continuous infusion of regular insulin (Humulin S, 60 mU/kg/min) plus a variable infusion of 20% dextrose. Using this technique, the blood glucose concentration was reduced in 40 minute steps aiming for 5, 3.8, 3.3, 2.8 and 2.4 mM respectively (the latter step was only 20 minutes).

Taking breath samples

Volunteers provided breath samples directly into the Breathotron and into Nalophan sample bags (Air Products UK Ltd) for later analysis by SIFT-MS at each time point (i.e at the baseline blood level at the start and at each glucose clamp step). Thus breath samples were taken at 30 minutes into each of the 40 minute stages of the target blood glucose concentrations. The final stage of the clamp nominally at 2.2mM blood glucose lasted for only 20 minutes due to the fact this was at too low a level to maintain for 40 minutes and breath samples were taken at the end of the stage. The breath samples in the Nalophan bags were stored together in a black plastic bag and taken to the laboratory for analysis by SIFT-MS a few hours later. It had previously been shown that there was little loss of acetone from Nalophan bags over this time period (Turner et al., 2012).

Blood glucose analysis

Plasma glucose concentrations were measured at five minute intervals using a Yellow Springs Instruments (YSI) analyser to enable the exact concentration to be correlated with the time of each breath sample.

SIFT-MS analysis

SIFT-MS has been described in detail previously (Smith and Španěl, 2005) so only a brief summary is given here. In SIFT-MS precursor ions (H_3O^+ , NO^+ and O_2^+) are produced from air and water vapour in a microwave discharge and are selected by a quadrupole mass filter. They are then injected into a fast flowing helium carrier gas, reacting with the trace gases and volatile organic compounds in the breath sample.. The precursor and product ions in the carrier gas pass into a second quadrupole mass spectrometer and detector for analysis. Data may be obtained through scanning a spectrum at a user-defined range of m/z values or by sampling individual ions. Acetone reacts with all three precursor ions, and in this study, analysis of acetone was carried out using the both H_3O^+ and NO^+ precursor ions (as described in Turner et al., 2009) to provide additional checks on the data obtained.

Results:

Breathotron: Testing of the Breathotron with different concentrations of three common breath volatiles - acetone, ammonia and propanol, over the range (0 – 10 ppmv) resulted in the responses (ΔR_{max}) of the MMOS which are shown in Figure 4. The sensor's response to all three compounds was linear over the range investigated. The responses for acetone and propanol were of similar magnitude while that for ammonia, although also linear, was very much smaller. In fact, ammonia barely caused a change in sensor resistance, so it is unlikely to be able to reliably detect ammonia in breath.

SIFT-MS results in glucose clamp

Results showing the relationship between breath acetone (as measured by SIFT-MS) and blood glucose in this clamp study for each of the 8 diabetics tested in this study are recorded in Turner et al. (2009) so will not be repeated here. However, it is clear that although the acetone concentrations at each blood glucose concentration differ

greatly between each volunteer, the data for individual volunteers exhibits a linear decrease in breath acetone with as the blood glucose concentration is reduced. Figure 5 shows this for one volunteer in the glucose clamp study. Propanol, which gives a similar magnitude MMOS signal to acetone was not detected in appreciable quantities in the breath samples taken.

Breathotron results from glucose clamp

Breathotron samples were obtained contemporaneously with those intended for analysis by SIFT-MS, and the ΔR_{\max} values at each blood glucose concentration are shown in Figure 6. As can be seen from these graphs, it is clear that there is a linear relationship between blood glucose concentration and ΔR_{\max} response of the Breathotron for each of the 8 individuals throughout the glucose clamp and at different blood glucose concentrations, with the exception of subject e). In comparison with those in Turner et al. (2009), all are similar except for e). This implies that the signal from the Breathotron is not dependent upon acetone alone and that other VOCs may also be contributing to the signal, although analysis of the SIFT-MS data did not indicate what this other compound could be; there was certainly not very much propanol present in the breath of these subjects during the clamp. Despite this, for seven out of the eight subjects, there was a clear positive linear relationship between sensor signal and blood glucose.

Figure 7 shows representative graphs of data from two volunteers of the Breathotron sensor response against breath acetone determined using SIFT-MS. Tests with the highest and lowest values of R^2 have been selected for display and the case with the highest value (upper panel of Figure 7) corresponds to the results shown in Figure 5. While a positive trend is observed in all cases, it is clear that the strength of the association varies considerably between individual tests.

Discussion:

Here, we have demonstrated that a portable breath sensing device (The Breathotron) has been able to monitor the breath of subjects with type 1 diabetes in a hypoglycaemic glucose camp. The signal from the Breathotron is correlated with acetone as measured by SIFT-MS (Figure 6), and also with blood glucose. The correlation was positive for ΔR_{\max} against blood glucose for seven out of eight

subjects in comparison with eight out of eight for the corresponding data from SIFT-MS. In the one subject where the correlation between blood glucose and ΔR_{\max} was negative, it indicates that acetone was not solely responsible for the entire MMOS signal.

Although it has been shown that end-tidal breath samples are the most accurate in quantifying breath VOCs (King et al. 2009), acetone is well represented by whole breath and differences do not affect the results of this study.

There were some differences in the acetone/Breathotron signal correlations for one subject. Here, the correlation between between glucose concentration and acetone determined by SIFT-MS was weakest out of all the volunteers. In fact the breath acetone concentration was around 600 ppbv at both the highest and lowest values of glucose recorded, with a nadir at around 400 ppbv in the mid-range. This suggests that, at least to some degree, a real physiological phenomenon is being observed.

Although this shows promise as a method for monitoring blood glucose, the relationship between blood glucose concentration and sensor response expressed as ΔR_{\max} clearly differs quantitatively between individuals. However it remains possible that each individual will have a relationship which is specific to themselves (Turner et al., 2009; Turner et al., 2011). If there are other compounds contributing to the observed correlations, sensor-based instruments such as the Breathotron are not themselves a suitable means of determining either their identity or abundance. Research into seeking compounds in breath that may be used to monitor blood glucose requires more sophisticated analytical equipment such as SIFT-MS which can directly speciate and determine volatile organic compounds found in breath.

Despite this, portable breath analysis devices have the potential to be convenient, non-invasive, robust and inexpensive compared with the lifetime cost of a blood glucose biosensor and associated glucose testing strips. Such devices seem unlikely to totally replace the need for blood glucose monitoring, but may be useful to warn of impending hyper- or hypo-glycaemic episodes or to enable increased sampling frequency giving better overall control of glycaemia. This may be of particular value for hypo-unaware sufferers for whom the consequences of a hypoglycaemic attack are potentially catastrophic.

Acknowledgements

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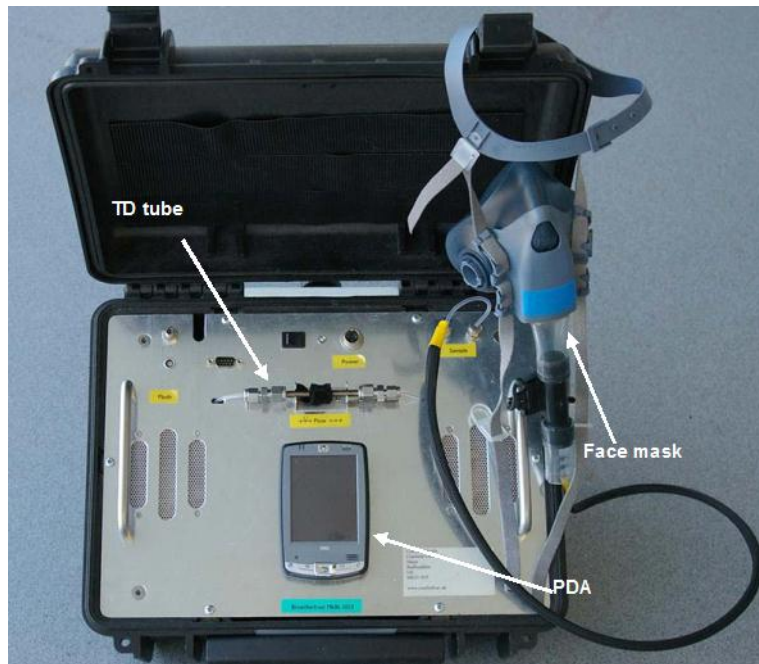


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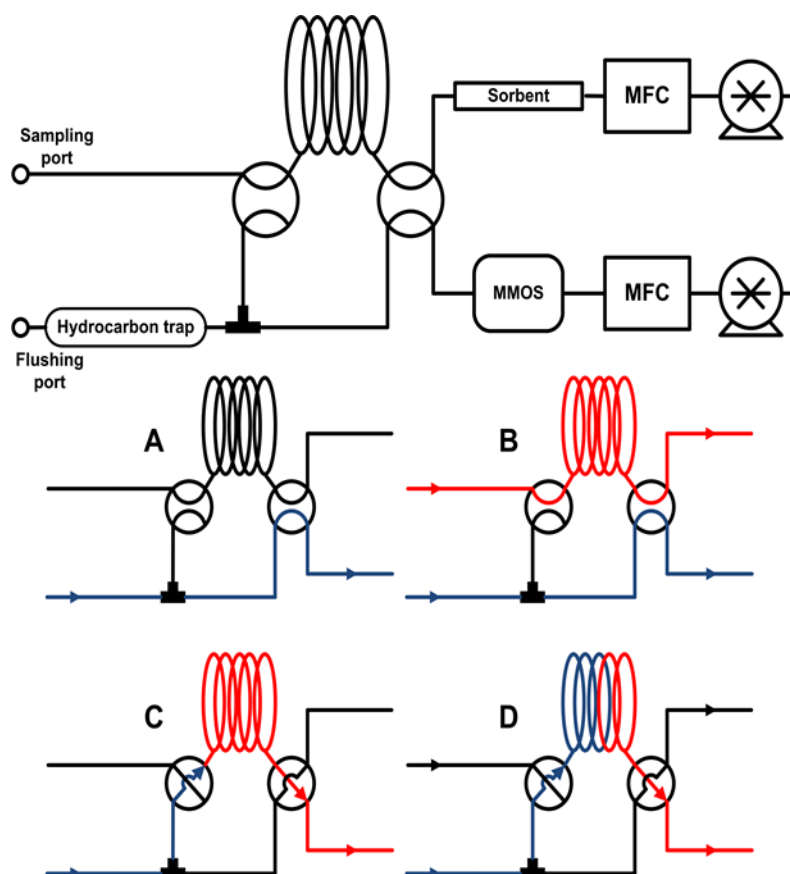


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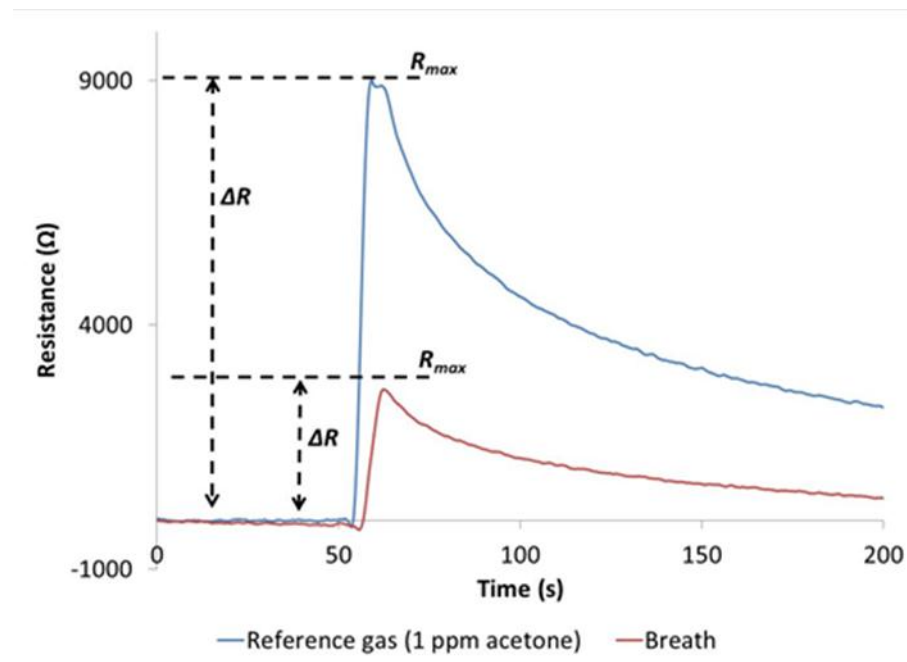


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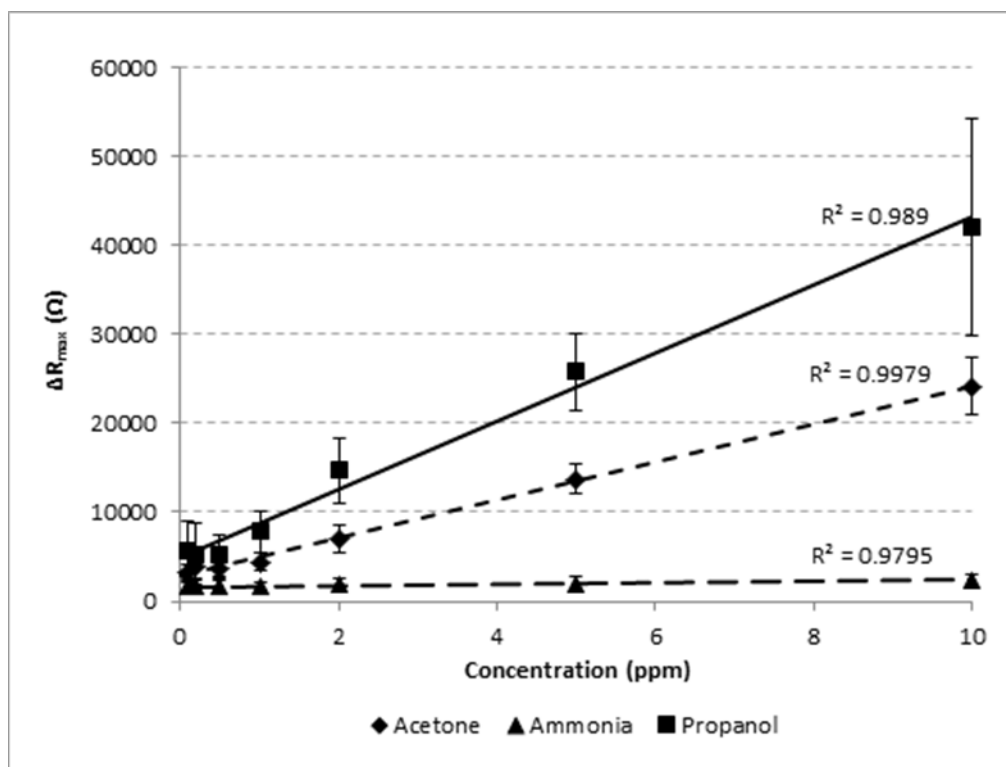


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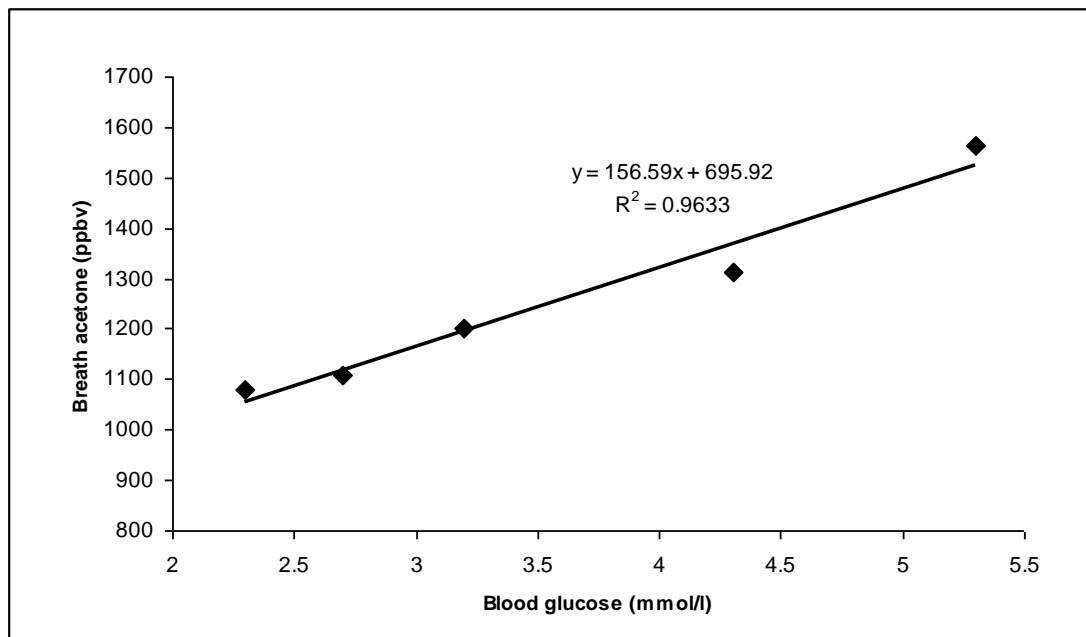


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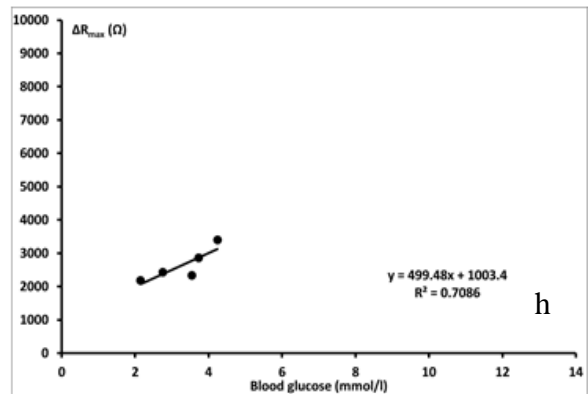
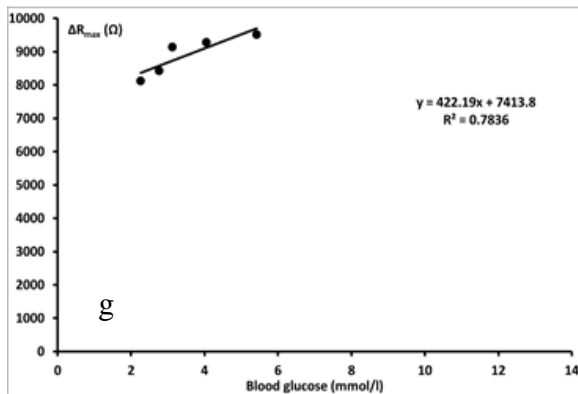
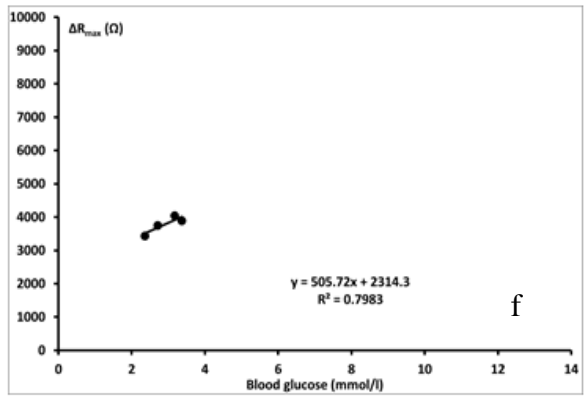
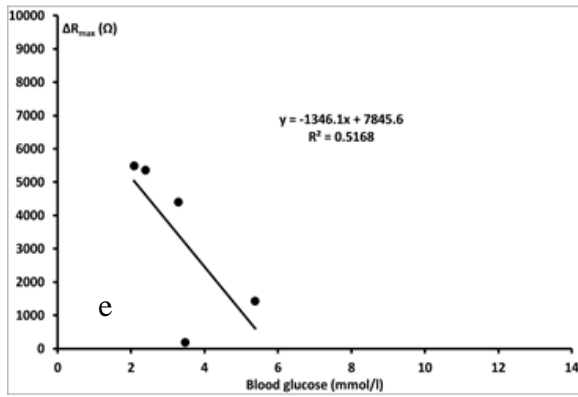
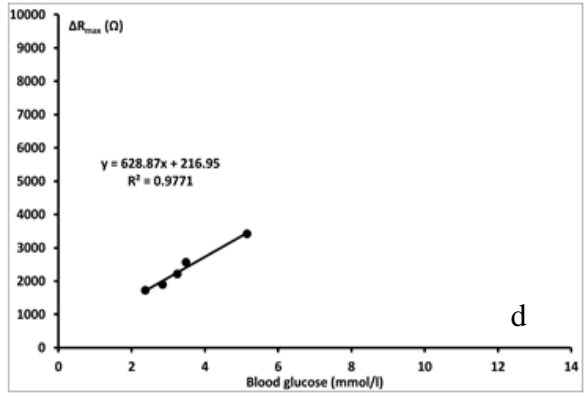
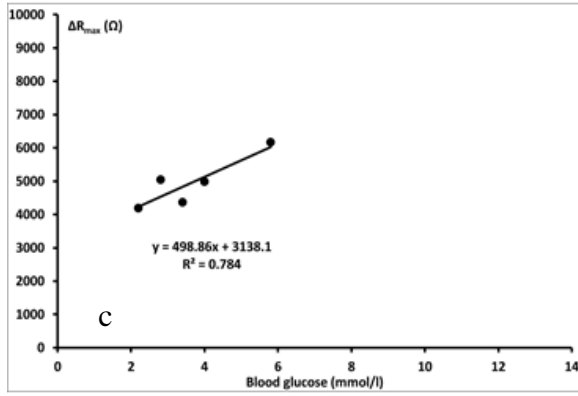
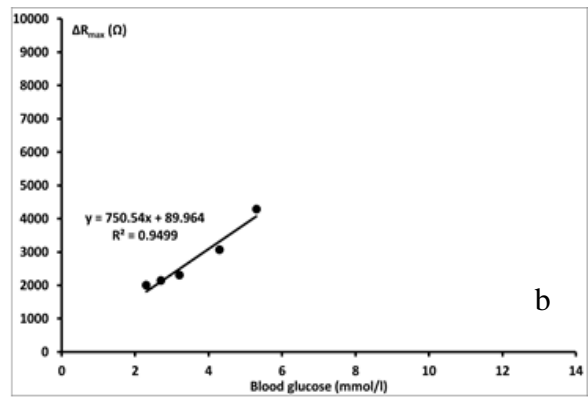
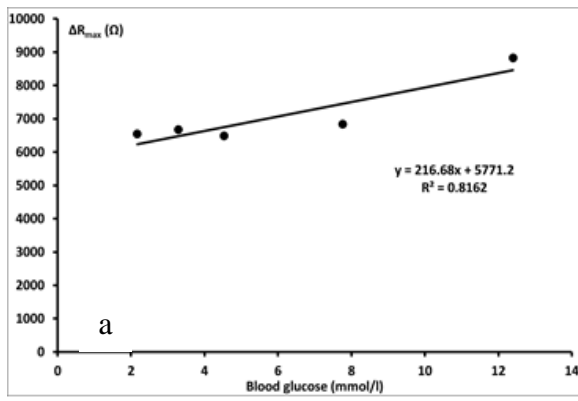


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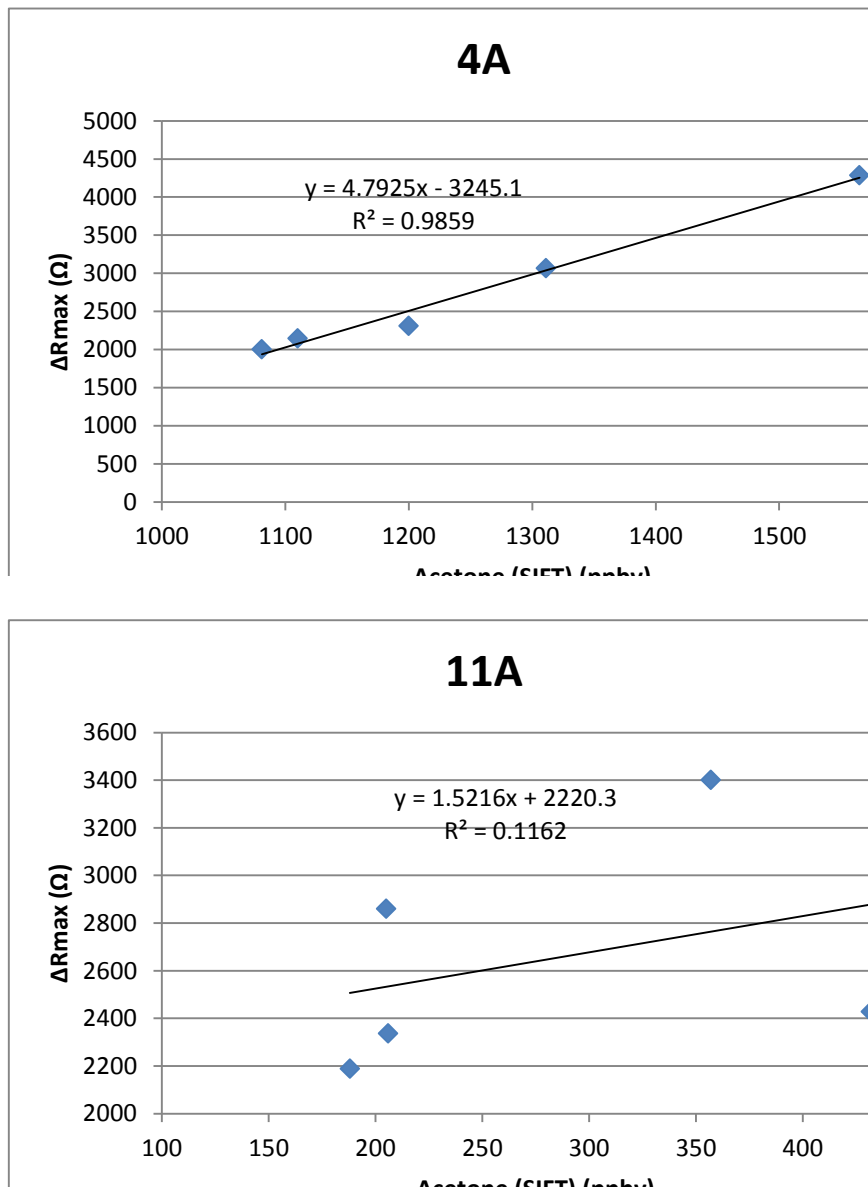


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